REMARKS

Status of the Claims

Claims 1-20 are pending. Claims 2, 4-17 and 19-20 are canceled. Claims 1-4 and 18-20 are rejected. Claims 1, 3 and 18 are amended herein. No new matter is added.

Claim amendments

Pending claims 2, 4, 19 and 20 are canceled. Claims 1 and 18 are amended to overcome rejections under 35 §U.S.C. 112, first paragraph and 35 §U.S.C. 103. Specifically, claims 1 and 18 are amended by incorporating limitations of a transgenic mouse and of an E2F1 promoter recited in dependent claims 2 and 4 and dependent claims 19 and 20, respectively. Additionally, claim 1 is amended to incorporate the limitation of a luciferase recited in dependent claim 3. Claims 3 and 18 are amended to recite that the luciferase is firefly luciferase.

The 35 U.S.C. §112, First Paragraph Rejection

Claims 1-4 and 18-20 are rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. Applicant respectfully traverses this rejection.

The Examiner states that the specification does not provide enablement for the claims as written originally, but provides enablement for

making an Elux mouse, having cells comprising the firefly luciferase transgene operably linked to an E2F1 promoter.

Applicants have canceled claims 2, 4, 19 and 20. As discussed supra, amended claims 1 and 18 incorporate the limitations of claims 2 and 4 and of 19-20, respectively. Amended claims 1 and 18 are directed to a transgenic mouse expressing a reporter gene coding for a luciferase or a firefly luciferase, respectively, where the reporter gene is operably linked to E2F1 promoter.

The specification teaches a transgenic mouse expressing a fusion construct comprising E2F1 promoter that is operably linked to a gene encoding a luciferase protein (pg. 24, ll. 4-19; Fig. 2). What is novel and non-obvious in the instant invention is the use of the E2F1 promoter, which is regulated by cell cycling, as a means to monitor, *inter alia*, tumor progression or regression, via a bioluminescent response generated by a luciferase co-propagated with the promoter. The use of firefly luciferase is simply one embodiment reflecting its common usage in bioluminescent systems.

One of ordinary skill in the art would recognize that a bioluminescent system is defined and known in the art as requiring an enzyme, generically called a luciferase, to catalyze a reaction to produce light from a substrate molecule, generically called a luciferin. A bioluminescent system using firefly luciferase, as demonstrated in the instant invention, is not distinct from one using, for example, *Renilla* luciferase, as disclosed in Bhaumik and Gambhir (PNAS 99(1):377-382, 2002) cited by the Examiner for the purposes of the instant invention. Both

systems generate detectable light from the catalytic action of the luciferase on the luciferin.

The specification teaches that, although most luciferases have peak emission at 400-590 nm, the emission spectrum is sufficiently broad to extend to red wavelengths of greater than 600 nm that allows signal detection throughout the entire body of the mouse (pg. 18, ll. 2-13). Additionally, imaging via a CCD camera using cooled scientific grade arrays, allows for observation of bioluminescent cells from 1-3 cm beneath the surface and for signal detection down to a few photons per pixel (pg. 18, ll. 14 to pg. 19, ll. 9). Bioluminescent imaging via CCD cameras also provides for continuous real time imaging. This certainly overcomes any potential imaging problems due to differences between the emission spectra of luciferases.

Thus, any commercially available luciferase gene may be ligated to E2F1 promoter using standard ligation techniques. Provided that the appropriate luciferin was available as substrate, upon administration of the luciferin to the transgenic mouse, bioluminescence will be triggered in cycling cells and will be detectable using the real time imaging techniques described and standard in the art. Luciferase genes and corresponding luciferin proteins are commercially available through several companies, including Xenogen and LUX Biotechnology.

Applicants submit that, as amended, the scope of the claims is commensurate with the enablement provided in the specification of the instant invention. Hence, in view of what is known and standard in the art, the guidance provided by the instant specification is sufficient for one skilled in the art to make

and use the invention, as claimed in amended claims 1 and 18. Accordingly, in view of the amendments and arguments presented herein, Applicants respectfully request that the rejection of claims 1, 3 and 18 under 35 U.S.C. 112, first paragraph, be withdrawn.

Claims 1-3 and 18-19 are rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description requirement. Applicants respectfully traverse this rejection.

In response to the Examiner's comments regarding promoter of the claims being broad in scope, Applicants have canceled claims 4 and 20 and restricted claims 1 and 18 to E2F1 promoter. Applicant submits that the scope of the amended claims satisfy the Examiner's requirement and is commensurate with the written description in the specification. Accordingly, in view of the amendments and arguments presented herein, Applicant respectfully requests that the rejection of claims 1, 3 and 18 under 35 U.S.C. §112, first paragraph, be withdrawn.

Claims 1-2 and 4 are rejected under 35 U.S.C. §112, first paragraph, for failing to comply with the written description. Applicants respectfully traverse this rejection. Applicants respectfully traverse the rejection.

The Examiner states that the invention of claims 1-2 and 4 encompasses a non-human transgenic animal having cells comprising a reporter gene encoding any protein capable of producing light that is operably linked to a

cell-cycle-sensitive promoter. The Examiner states that the proteins of these claims are broad in scope, being defined on the basis of their effect and not on any specific structure (pg. 17, ll. 16-20) wherein the working example teaches the firefly luciferase gene. In considering luciferases, the Examiner states that the specification does not provide any disclosure as to what would have been the required structure which would allow one to distinguish the various species of the genera. The Examiner continues that because the genus of "luciferase" comprises such a large number of species, a sufficient number of representative examples would have to be described to provide an adequate written description.

Applicant has canceled claims 2 and 4. Applicant has amended claim 1, as discussed supra, to recite a transgenic mouse comprising a reporter gene encoding a luciferase operably controlled by an E2F1 promoter. Applicant maintains that the specification enables one of ordinary skill in the art to generate a transgenic mouse having cells with a reporter gene encoding a luciferase operably controlled by and co-propagated with an E2F1 promoter. As luciferase genes and their corresponding luciferin proteins are known and commercially available, the structural differences between the various luciferase genes and the corresponding luciferin proteins need not be contained in a written description. It is well settled that a patent specification need not detail and preferably omits, what is known or understood in the art. Accordingly, in view of the amendments and arguments presented herein, Applicant respectfully requests that the rejection of claim 1under 35 U.S.C. §112, first paragraph be withdrawn.

The 35 U.S.C. §103(a) Rejection

Claims 1-3 and 18-19 are rejected under 35 U.S.C. §103(a) as being unpatentable over **Hasan** *et al.* (Genesis 29:116-122, 2001) in view of **Muller** *et al.* (Mol Cell Biol 20(9): 3316-3329, 2000). Applicants respectfully traverse this rejection.

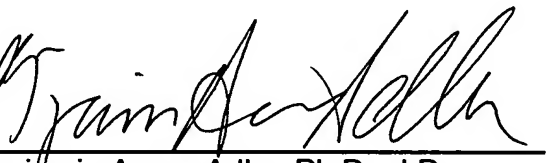
Applicants would like to respectfully point out that the teachings of **Hasan** *et al.* as cited by the Examiner are in fact teachings of **Vooijs** *et al.* (Genesis 29:116-122, 2001). However, as discussed supra, Applicant has incorporated the limitation of the E2F1 promoter recited in dependent claims 4 and 20 into independent claims 1 and 18, respectively. As this limitation is not rejected as being obvious over the combination of Hasan et al. and Vooijs et al. then neither are independent claims 1 and 18, amended to incorporate this limitation obvious over the combination.

Claims 2 and 19 originally depended from claims 1 and 18 and limited the transgenic animal to a mouse. Claims 2 and 19 are canceled. The incorporation of these limitations into claims 1 and 18 does not render claims 1 and 18 obvious, because amended claims 1 and 18 are still not obvious over Hasan et al. with Vooijs, absent these further limitations. Amended claim 3 depends from amended claim 1 and limits the luciferase to firefly luciferase and also is not obvious over the prior art because amended claim 1 is not obvious. Accordingly, in view of the amendments and arguments presented herein, Applicants respectfully request the withdrawal of rejection of claims 1, 3 and 18 under 35 U.S.C §103(a) be withdrawn.

This is intended to be a complete response to the Office Action mailed November 19, 2004. Applicants submit that the pending claims 1, 3 and 18 are in condition for allowance and respectfully request that these claims be passed to issuance. If any issues remain outstanding, please telephone the undersigned attorney of record for immediate resolution. Applicants enclose a Petition for a One Month Extension of Time. Please credit the credit card identified on the enclosed Form PTO-2038 for the $60 petition fee. Please debit any insufficiency in the fees from Deposit Account No. 07-1185 upon which the undersigned is allowed to draw.

Respectfully submitted,

Date: March 18, 2005



Benjamin Aaron Adler, Ph.D., J.D.
Registration No. 35,423
Counsel for Applicant

ADLER & ASSOCIATES
8011 Candle Lane
Houston, Texas 77071
(713) 270-5391 (tel.)
(713) 270-5361 (facs.)
badler1@houston.rr.com